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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/700,590
Filing Date: April 16, 2001
Appellant(s): TANG ET AL.

Michele M. Simkin
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 1 April, 2004.A statement identifying the real party in interest is contained in the brief.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Invention

The summary of invention contained in the brief is correct.

(6) Issues

The appellant's statement of the issues in the brief is correct.

(7) Grouping of Claims

Appellant's brief includes a statement that claims 23-29 and 31do not stand or fall together and provides reasons as set forth in 37 CFR 1.192(c)(7) and (c)(8).

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Prior Art of Record

5807522 Brown et al., 9-1998

Brenner et al., "Assessing sequence comparison methods with reliable structurally identified distinct evolutionary relationships", Proc. Nat. Acad. Sci. Vol.95 (1998), pp.6073-6078.

French et. al. , "BRD4 bromodomain Gene Rearrangement in Aggressive Carcinoma with Translocation t (15;19)" Am. J. Pathol., Vol.159 (2001), pp. 1987-1992.

Lashkari et al., "whole genome analysis: Experimental access to all genome sequenced segments through larger-scale efficient oligonucleotide synthesis and PCR", Proc. Nat. Acad. Sci. Vol.94 (1997), pp.8945-8947.

Maruyama et al., " A Mammalian bromdomain Protein, BRD4, interacts with replication factor C and inhibits progression to S phase," Mol. Cell. Biol., Vol. 22 (2002), pp. 6509-6520.

Ngo et al., The Protein Folding Problem and Tertiary Structure Prediction, (1994), pp.492-495.

Nuwaysir et al., "Microarrays and Toxicology: The advent of Toxicogenomics" Molecular Carcinogenesis, Vol. 24 (1999), pp. 153-159.

Ostrowski et al., "Stimulation of p85/RING3 kinase in multiple organs after systemic administration of mitogens into mice" Oncogene, Vol.16 (1998), pp.1223-1227.

Rockett et al., "Differential gene expression in drug metabolism and toxicology: practicalities, problems and potential", Xenobiotica Vol. 29(7) (1999), pp. 655-691.

Rockett and Dix, "Application of DNA arrays to toxicology" Environ. Health Perspect, Vol.107 (1999) pp. 681-685

Steiner and Anderson, "Expression profiling in toxicology-potentials and limitations", Toxicology Letters, Vol.112-113, (2000), pp.467-471

Wells et al., Aditivity of Mutational Effects in Proteins, Biochemistry, Vol. 26, No:37 (1990), pp.8509-8517.

Scott et al., " The Pendred syndrome gene encodes a chloride-iodide transport protein," Nature Genetics, Vol.21 (1999), pp. 440-443.

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

ISSUES ONE AND TWO: Claims 23-29 and 31 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility.

The instant claims are directed to polynucleotide encoding a polypeptide of SEQ ID NO: 22 belonging to a human transmembrane protein (pages 10-13). These claims are drawn to an invention with no apparent or disclosed patentable utility. The instant application has provided a partial description of the isolated protein in the form of a predicted amino acid sequence. However, the application does not disclose the physical or structural properties of this protein. In addition, the instant application does not disclose the biological role of this protein or its significance.

It is clear from the instant specification that the claimed nucleotides encode peptides that have consensus sequences or specific domains that are *homologous* to nucleotides of various protein families based on various analytical methods including BLAST and PRINTS (see Tables 1-4, pages 72-105). However, the homology of a peptide is not a reliable indicator for the functional characteristics (see Scott et al. 1999). Even if proteins share considerable homology because of their evolutionary origins they often do not share any functional homology. Further characterization is required to identify a patentable utility and this further characterization is part of the act of invention and, until it has been undertaken, Applicants' claimed invention is incomplete.

The instant situation is directly analogous to that of which was addressed in *Brenner v. Manson*, 148 U.S.P.Q. 689 (Sus. Ct, 1966), in which a novel compound which was structurally analogous to other compounds which were known to possess anticancer activity was alleged to be potentially useful as an antitumor agent in the absence of evidence supporting this utility. The court expressed the opinion that all chemical compounds are "useful" to the chemical arts when this term is given its broadest interpretation. However, the court held that this broad interpretation was not the intended definition of "useful" as it appears in 35 U.S.C. 101, which required that an invention must have either an immediate obvious or fully disclosed "real-world" utility. The court held that:

> "The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility," "[u]nless and until a process is refined and developed to this point - where specific benefit exists in currently available form - there is insufficient justification for permitting an applicant to engross what may prove to be a broad field," and "a patent is not a hunting license," "[i]t is not a reward for the search, but compensation for its successful conclusion."

The instant claims are drawn to polynucleotides, which have a yet undetermined function or biological significance. Appellants have disclosed that they are in possession of a polynucleotide encoding an allegedly novel protein of SEQ ID NO: 22. However, there is no actual and specific significance that can be attributed to said novel polypeptides or the nucleotides identified in the specification, except the prophetic recitation of potential uses, which include the use in diagnosis, treatment, or prevention of immune, reproductive, smooth muscle, neurological, gastrointestinal, developmental, and cell proliferative disorders (page 23, lines 26-30). Furthermore, the nucleotides of the instant invention have not been linked to a disease state methods of treating diseases listed in page 37, line 25 to page 40, line12. For these reasons, the instant invention is incomplete. Since, neither the prior art nor the specification provides for the physiological significance of the disclosed and claimed novel nucleotides encoding the proteins, there is no immediately obvious patentable use for it. In addition, the instant specification does not disclose a "real-world" use for said polynucleotides, except the prophetic recitation of potential uses, which include possible biological and therapeutic uses. Also, there are no working examples that demonstrate any specific utility. Thus, the claimed invention is incomplete and, therefore, does not meet the requirements of 35 U.S.C. 101 as being useful. Therefore, the polynucleotide of the invention is not supported by a specific and substantial asserted utility or a well-established utility.

Claim Rejections - 35 USC § 112, first paragraph

Claims 23-29 and 31 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

> Claims (whatever) are rejected also rejected under 35 U.S.C. 112, first paragraph, because the specification, were it enabling for ..., would still not be enabling for sequences of limited homology to ... or sequences comprising fragments of ..., with no functional limitation.

Claims 23, 26-28 and 31 are also rejected under 35 U.S.C. 112, first paragraph, because the specification, were it enabling only for, an isolated polynucleotide of nucleic acids encoding SEQ ID NO: 22 or nucleotides of SEQ ID NO: 101 and (possibly, depending upon the utility) a method of making the protein of SEQ ID NO: 101 would still not be enabling for sequences of limited homology to SEQ ID NO: 101 or SEQ ID NO: 22 or sequences comprising fragments of SEQ ID NO: 101 or SEQ ID NO: 22, with no functional limitation. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Even if a patentable utility were to be established, claims 23, 26-28 and 31 (depending upon whether the utility were predicated upon the use of the nucleic acid as a probe, or whether the utility was based upon use of the encoded protein), the specification would be found to be enabling only for an isolated polynucleotide of nucleic acids encoding SEQ ID NO: 22 or nucleotides of SEQ ID NO: 101 and (possibly,

depending upon the utility) a method of making the protein of SEQ ID NO: 101, but not to a polynucleotide sequence 90% identical to SEQ ID NO: 101 without regard to function, as recited in claim 31, nor to fragments. The specification, even if it did enable a nucleic acid having SEQ ID NO: 101 or which encodes SEQ ID NO: 22 would not be found to provide support commensurate in scope with the claims.

The specification discloses SEQ ID NO: 101, and postulates a protein having SEQ ID NO: 22 or fragment containing A80-N140 of SEQ ID NO: 22, encoded by such. No activities are ascribed to either the nucleic acid or the polypeptides. The state of the prior art is that both sequences are novel. Although the relative level of skill in the art is high, the claims are broad, and there are no working examples or guidance or direction to allow the person of ordinary skill in the art to make and use species in a manner commensurate in scope with the claims. Although the specification outlines art-recognized procedures for producing the variants, this is not adequate guidance as to the nature and function of the polynucleotides that can be identified, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. What is provided is thus the idea for an invention, *not the invention* itself. With particular respect to claims to nucleic acid which 'encodes' protein, if the nucleic acid were found to have utility as a hybridization probe, such would not be commensurate in scope with such claims, as the majority of such species would not be useful as hybridization probes. It is not recognized practice in the art to alter nucleic acid sequences from their naturally occurring sequences for use as hybridization probes in any method disclosed in the specification, e.g. microarrays. Accordingly, it would

require undue experimentation to determine how to use a commensurate number of species, even *if* nucleic acid of SEQ ID NO: 101 itself has utility, or *if* the protein of SEQ ID NO: 22 were found to have utility. Also, certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions may also be critical determinants of antigenicity. Although it is accepted that the amino acid sequence of a polypeptide determines its structural and functional properties, predicting a protein's structure and function from mere sequence data remains an elusive task. Thus, predicting which sequences *comprising fragments* would retain the functions of the protein is well outside the realm of routine experimentation. The amount of experimentation required to make and/or use the full scope of the claimed sequences would require trial and error experimentation to determine the functional sequences. In addition, the specification fails to disclose any structures beyond SEQ ID NO: 22 and SEQ ID NO: 101 that were identified. There is no guidance as to the nature of any other sequences meeting the limitations of the claims. Thus, the artisan would be unable to prepare the claimed polynucleotides and the specification fails to meet the requirement of teaching "how to make" the invention.

Claims 23, 26-28 and 31 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time

the application was filed, had possession of the claimed invention. *This is a written description rejection.*

The specification discloses the nucleotide encoding SEQ ID NO: 22, which includes sequence of SEQ ID NO: 101. This meets the written description provisions of 35 USC 112, first paragraph. However, the specification does not disclose a nucleic acid molecules encoding a polypeptide that is consisting of a amino acid sequence which is at least 90% identical to the amino acid sequence of SEQ ID NO: 22 or nucleic acid molecules encoding a polypeptide that is consisting of a amino acid sequence which is a biologically active fragment of the polypeptide sequence of SEQ ID NO: 22 or nucleic acid molecules encoding a polypeptide that is consisting of a amino acid sequence which is an immunogenic fragment of the polypeptide sequence of SEQ ID NO: 22. The claims as written, however, encompass nucleotide sequences which were not originally contemplated and fail to meet the written description provision of 35 USC 112, first paragraph because the written description is not commensurate in scope with the recitation of claim 23, 24 and 26-29 and 31. The specification does not provide adequate written description to support the genus encompassed by the instant claims.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (*See Vas-Cath* at page 1116).

With the exception of the nucleotide encoding SEQ ID NO: 22, which includes sequence of SEQ ID NO: 101, the skilled artisan cannot envision all the detailed

chemical structure of the claimed nucleic acid sequences, regardless of the complexity or simplicity of the method of isolation.

Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The polypeptide itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016. One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. In *Fiddes v. Baird*, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class.

Therefore, only the nucleotide encoding SEQ ID NO: 22, which includes sequence of SEQ ID NO: 101, but not the full breadth of the claims meets the written description provision of 35 USC 112, first paragraph. The species specifically disclosed are not representative of the genus because the genus is highly variant. As a result, it does not appear that the inventors were in possession of various polypeptide sequences set forth in claims 23,24 and 26-29 and 31.

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115.) Applicants are directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 64, No. 244, pages 71427-71440, Tuesday December 21, 1999.

(11) Response to Argument

Appellants' general remarks: At p. 4, last paragraph of the Brief, Appellants characterize the invention as a polynucleotide sequence corresponding to a gene that is expressed in human tissues and that codes for a polypeptide of SEQ ID NO: 22

(HTMPN-22) demonstrated in the patent specification to be a member of the class of Ring3-related bromodomain proteins, whose biological functions include regulation of transcription and cell growth. Based on the recited prophetic potential uses, Appellants urge that the claimed invention has numerous practical, beneficial uses in toxicology testing, drug development and diagnosis of disease, none of which requires the knowledge of how the polypeptide coded for by the claimed polynucleotide actually functions. Appellants state that the claimed invention already enjoys significant commercial success.

Appellants' arguments have been fully considered but are not found to be persuasive for several reasons. In the absence of any functional or biological significance of this protein, there is no immediately obvious "patentable " use for it. The specification only teaches that HTMPN-22 is a Ring3 protein (Table 2) and recites prophetic potential uses, which include the use in diagnosis, treatment, or prevention of immune, reproductive, smooth muscle, neurological, gastrointestinal, developmental, and cell proliferative disorders (page 23, lines 26-30).

The specification does not disclose that the claimed genes are markers for specific diseases. Absent a disclosure of altered levels or forms of a gene in diseased tissue as compared with the corresponding healthy tissue, the gene is not a disease marker or an appropriate target for drug discovery or toxicology testing. Finally, evidence of commercial success, while sometimes persuasive as secondary evidence of non-obviousness, is immaterial to utility and enablement. Many products have

enjoyed commercial success due to fads or clever advertising, wherein the products would not have met the legal standards for utility and enablement.

Beginning at p. 5, second paragraph, Appellants discuss the Bedilion declaration submitted under 37 CFR 1.132 with the response to Office Action of 3/25/2003. Appellants characterize the Bedilion declaration as describing some of the practical uses of the claimed invention in gene expression monitoring applications, thus allegedly demonstrating the examiner's position to be without merit. In particular, Appellants state that the Bedilion declaration describes how the claimed expressed polynucleotide can be used in gene expression monitoring systems that were well-known at the time of the invention, and how those applications are useful in developing drugs and monitoring their activity. Appellants quote from the Bedilion declaration, that states that microarrays containing SEQ ID NO: 22-encoding polynucleotide and SEQ ID NO: 101 polynucleotide would be a more useful tool than microarrays lacking same in connection with conducting gene expression monitoring studies on proposed or actual drugs for treating cell proliferative and immune disorders for such purposes as evaluating their efficacy and toxicity. Beginning at p. 4 of the Brief, Appellants criticize the examiner's position that the claimed polynucleotide cannot be useful without precise knowledge of its biological function. Beginning at p. 6, second full paragraph of the Brief, Appellants assert that the final Office Action is replete with new arguments and positions in a misplaced attempt to justify the rejections made under 35 U.S.C. §§ 101 and 112, first paragraph, particularly with regard to gene expression monitoring. Appellants characterize the alleged new positions and arguments as including (a) the Tang '590

application does not disclose that the claimed polynucleotides in monitoring gene expression is "not specific"; (b) the gene expression monitoring results obtained using SEQ ID NOS: 22-encoding polynucleotides are allegedly "not...informative" or otherwise insufficient to constitute substantial, specific and credible utilities for SEQ ID NO: 22 polypeptide. Appellants assert that the Office Action has also failed to acknowledge the disclosure at p.55, which is alleged to be relevant to this issue. Appellant explains that the Rockett declaration, Iyer declaration, Bedilion (second) declaration, exhibits, references and Appeal Brief were submitted after final Office Action in response to the allegedly new arguments and positions that were taken by the Examiner in the final Office Action.

Appellants' arguments have been fully considered but are not found to be persuasive. Regarding the merit of the argument, any new polynucleotide can be used in a microarray, and thus this asserted utility is not specific. It does not relate to any particular characteristic of the claimed polynucleotide. Also, the disclosure that HTMPN-22 is structurally related to class of Ring3-related bromodomain protein genes does *not* render the asserted utility specific, since the specification does not establish that HTMPN-22 is expressed in any diseased tissues in any way that is different from the way it is expressed in healthy forms of the same tissues. In other words, the specification does not disclose that HTMPN-22 is expressed in specific tissues involved in regulation of transcription and cell growth at altered levels or forms. Thus, it is not a target for drug development, toxicology studies, or disease diagnosis. Significant further research would have to be conducted to identify diseases states, which correlate

with altered levels or forms of the claimed polynucleotides. Therefore, this asserted utility is also not substantial.

Appellants are further mischaracterizing the examiner's position. A specification can meet the legal requirements of utility and enablement for a new polynucleotide as long as the specification discloses a credible, specific and substantial asserted utility for the new polynucleotide, or a well-established utility for the claimed polynucleotide. A hypothetical example may serve to clarify. For example, a hypothetical specification discloses that a claimed polynucleotide is expressed in colon cancer and not expressed in healthy colon tissue. The hypothetical specification does not disclose the biological activity of the polypeptide encoded by the polynucleotide. The claimed polynucleotide in the hypothetical example would not be rejected under 35 U.S.C. §§ 101 and 112, first paragraph, as it has utility and is enabled as a colon cancer marker. However, such is not the fact pattern here. The instant specification discloses that the claimed polynucleotides are structurally related to class of Ring3-related proteins and hypothesizes that the claimed polynucleotides are involved in disorders associated with transcriptional regulation and cell growth, but the expression of the polynucleotides in diseased tissues and the corresponding healthy tissues was not evaluated. Therefore, there is no disclosure that the claimed polynucleotides are expressed at altered levels or forms in any specific, diseased tissue. It is noted that the instant application was filed 16 April 2001. No evidence has been brought forth during the prosecution history regarding the expression levels in diseased or healthy tissue. Also, no evidence has

been brought forth that the claimed polynucleotides encode polypeptides having specific cell growth or regulation of transcription activities.

Appellants' arguments with respect to new arguments have been fully considered but have not been found to be persuasive, and therefore the new declarations, exhibits, and references have not been considered. First, it is important to clarify that the final Office Action contained no new grounds of rejection. Any new positions or arguments put forth in the final Office Action were made only in response to Appellants' response of 26 June 2003. Furthermore, the non-final Office Action of 25 March 2003 clearly stated that the specification does not support a credible, specific and substantial utility regarding the claimed polynucleotides encoding SEQ ID NO: 22 and variants thereof for purposes unrelated to the asserted biological activity (see pp. 4-6). All of Appellants' subsequent arguments regarding toxicology and gene expression monitoring using microarrays (used in drug discovery research and toxicology studies), and the examiner's responses thereto were based on that statement. Therefore, the arguments and positions characterized by Appellants as new were not new. Regarding p.55 of the specification, it is true that p.55 discusses general gene expression monitoring approaches such as microarrays, which are used in drug discovery research and toxicology studies. However, toxicity testing is not specifically discussed. Also, since the disclosure does not disclose specific diseases, which should be treated with the protein, drug discovery and determining toxicity levels would have been quite meaningless.

I. The applicable legal standard.

Beginning at p. 9 of the Brief, Appellants summarize case law on the utility requirement. The essential disagreement appears to be the interpretation of what constitutes a specific, substantial and credible utility, as will be explained more fully below.

II. Toxicology testing, drug discovery, and disease diagnosis are alleged to be sufficient utilities under 35 U.S.C. §§ 101 and 112, first paragraph.

A. The uses of the SEQ ID NO: 22 (HTMPN-22) encoding polynucleotides for toxicology testing, drug discovery, and disease diagnosis are alleged as practical uses that confer "specific benefits" to the public:

Appellants argue at pages 10-14 of the Brief that the use of HTMPN-22 for toxicology testing, drug discovery, and disease diagnosis are practical uses that confer specific benefits to the public. Appellants state that there is no dispute that the claimed invention is a useful tool in cDNA microarrays used to perform gene expression analysis. Appellants assert that such is sufficient to establish utility for the claimed polynucleotide. Appellants refer to the Bedilion declaration as explaining the many reasons why a person skilled in the art reading the instant application would have understood that application to disclose the claimed polynucleotide to be useful for a number of gene expression monitoring applications, such as a probe for expression of the polynucleotide in connection with the development of drugs and the monitoring of the activity of such drugs. The Bedilion declaration discusses microarrays and Northern

analysis for measuring such. Specifically, Appellants quote from the Bedilion declaration that a person skilled in the art would have been able to use the claimed polynucleotide in gene expression monitoring to develop new drugs for the treatment of cell proliferative/growth and immune disorders. Beginning at the second paragraph of p. 11 of the Brief, Appellants refer to the opinion of Dr. Bedilion that a person skilled in the art at the time of the invention would have concluded that a cDNA microarray containing the claimed polynucleotide would be a more useful tool than a microarray lacking the claimed polynucleotide in connection with conducting gene expression monitoring studies on proposed or actual drugs for treating cell proliferative/growth or immune disorders for such purposes as evaluating the efficacy and toxicity. At the top of p. 12, Appellants discuss the Bedilion declaration's detailed explanations of how cDNA technology can be used to conduct gene expression monitoring evaluations. Appellants point to Dr. Bedilion's pages of text and numerous subparts explaining the importance of this technology. Appellants point to Dr. Bedilion's explanation that those skilled in the art at the time of the invention without any doubt would have appreciated the criticality of toxicity testing. Appellants urge that the Bedilion declaration establishes that persons skilled in the art, guided by the instant specification, at the time of the invention would have wanted their cDNA microarrays to comprise the claimed polynucleotide, because a microarray comprising the claimed polynucleotide would provide more useful results in the kind of gene expression monitoring studies than microarrays lacking the claimed polynucleotide.

At the bottom of p. 12 of the Brief, Appellants argue that the examiner does not address the fact that, as described on p. 55 of the specification, the claimed polynucleotide can be used as highly specific probes to measure both the existence and amount of complementary mRNA sequences known to be present in expression products of the claimed polynucleotides. Appellants conclude that the claimed invention is not, in that regard, some random sequence whose value, as a probe is speculative or would require further research to determine. At p. 13 of the brief, Appellants argue that, given that the claimed polynucleotides are known to be expressed, its utility as a measuring and analyzing instrument for expression levels is as indisputable as a scale's utility for measuring weight. Appellants review case law pertinent to the patentable utility of research tools. At the middle of p. 13 of the Brief, Appellants argue that there can be no reasonable dispute that persons skilled in the art have numerous uses for information about relative gene expression including understanding the effects of a potential drug for treating cell proliferative/growth and immune disorders. Appellants urge that, since the specification discloses the claimed polynucleotide to be expressed in cancer and immortalized cell lines, and the fact that the claimed polynucleotide is structurally related to other Ring3-related bromodomain proteins known to be associated with cell proliferative/growth and immune diseases, the skilled artisan would have derived more information about a potential cell proliferative or growth and immune disorder drug candidate or potential toxin with the claimed invention than without it. At the top of p. 14 of the Brief, Appellants refer to Dr. Bedilion's discussion of the Brown et al. Patent (U.S. 5807522), attached to the declaration. Dr. Bedilion characterizes the

patent as providing evidence that microarrays can be used in numerous genetic applications, including monitoring of gene expression in different tissue types, disease states, in response to drugs, and in response to potential toxins. Appellants refer to other publications that discuss microarrays and gene expression technology with respect to drug screening and toxicology testing at pp. 12-14 of the Brief.

Appellants' arguments have been fully considered but have not been found to be persuasive. While the examiner agrees that any polynucleotide, including the claimed polynucleotides, can be used in a cDNA microarray, such does not confer patentable utility on the claimed polynucleotides. Since any polynucleotide can be used in a microarray, such a use is not specific to the claimed polynucleotides. Just as any orphan receptor can be used in an assay to screen for ligands, such does not confer patentable utility on a particular orphan receptor. Such can be done with any orphan receptor, and thus the asserted utility is not specific. Furthermore, since the specification does not disclose a correlation between any disease or disorder and an altered level or form of the claimed polynucleotides, the results of gene expression monitoring assays would be meaningless without significant further research. Therefore, the asserted utility is also not substantial.

The instant specification does not substantiate a link between the claimed polynucleotides and any specific cell proliferative/growth or immune disorder. The specification merely discloses that the claimed polynucleotides are structurally related to Ring3-related proteins, and that they are expected to be involved in cell proliferative/growth and immune processes (and thus, disorders). The specification

does not disclose the results of the required control in order to draw any conclusions regarding disease, namely, that the claimed polynucleotide is not expressed (or is expressed at an altered level or form) in the corresponding healthy tissues. Thus the presence of this polynucleotide is not diagnostic for any disease. In addition, many genes expressed in diseased tissues have nothing whatsoever to do with the disease and are not targets for drug development or toxicology. For example, actin and histone genes are expressed in normal and diseased tissues; they are constitutively expressed in all tissues. These are not suitable targets for drug development or toxicology studies, since disruption of these genes would kill the patient.

Additionally, the instant specification has not established that the claimed polynucleotides are expressed at altered levels or forms in diseased tissue as compared with the corresponding healthy tissue. If the claimed polynucleotide were in a microarray and a compound caused decreased expression of the claimed polynucleotide, what would that mean to the skilled artisan? Is it a potential drug, or would administering the compound be likely to acerbate the disease? The claimed polynucleotides may very well be expressed at equivalent levels in healthy tissues. If that were the case, then the compound would not be a good potential drug. The claimed polynucleotides may also very well be expressed at a lower level in a particular cell proliferative/growth or immune diseased tissue as compared to the corresponding healthy tissue. Then a compound that decreased the expression of the claimed polynucleotides would not be a good potential drug. Evidence of a differential expression might serve as a basis for use of the claimed polynucleotide as a diagnostic

for a disease. However, in the absence of any disclosed relationship between the claimed polynucleotide or the protein that is encoded thereby and any disease or disorder, any information obtained from an expression profile would only serve as the basis for further research on the observation itself. "Congress intended that no patent be granted on a chemical compound whose sole 'utility' consists of its potential role as an object of use-testing." *Brenner v. Manson*, 148 USPQ at 696. The disclosure does not present a substantial utility that would support the requirement of 35 U.S.C. §101.

There is no doubt that cDNA microarray technology is an extremely valuable technique in gene expression monitoring, toxicology testing, and drug efficacy testing. However, the claims are not drawn to the technique. The claims are directed to polynucleotides, which have not been disclosed as being associated with any particular disease or condition by its being expressed at an altered level or form in diseased tissue as compared to the corresponding healthy tissue. Any such polynucleotide could be added to a microarray. Thus, this asserted utility is not specific. Determining the relationship between the claimed polynucleotides and any specific disease or disorder would require significant further research. Therefore, this asserted utility is also not substantial.

Adding the claimed polynucleotide to a microarray would not make the microarray any more valuable than adding any other "orphan" polynucleotide. The asserted utility is not specific to the claimed polynucleotide. Any polynucleotide is a highly specific probe for itself or its complement, or any mRNA that can be transcribed

from it. Such can be said for any polynucleotide. Thus, this asserted utility is not specific or substantial.

Appellants' analogy *to* a scale is misplaced. It is true that a scale has patentable utility as a research tool. However, the object being weighed on the scale does not necessarily have patentable utility. In the instant case, microarray technology has patentable utility. However, the microarray is not being claimed, but rather a polynucleotide that can be used in microarrays. The claimed polynucleotide is not disclosed as being expressed at an altered level or form in any diseased tissue as compared to the corresponding healthy tissue. Therefore, the assertion that the claimed polynucleotide has patentable utility as a probe in, or member of, a microarray is not specific. Any orphan polynucleotide can be used in the same way.

The fact that the gene is expressed in cancer cells and is structurally related to Ring3 does not provide it with a utility as a probe. *The* specification does not disclose that the claimed polynucleotide is expressed at an altered level or form in any particular disease or disorder as compared to the corresponding healthy tissues. It may be useful to consider how broad the term "cell proliferative/growth disorders or immune disorders" is. Cell proliferative disorders include cancers, psoriasis, warts and slow-closing wounds. Immune disorders include arthritis, inflammatory bowel disease, and asthma. Even if it could be assumed that the claimed polynucleotides play a role in a cell proliferative/growth or immune disorder, determining which disorders are involved and how the claimed polynucleotides are altered during the disorder requires significant further research.

The Brown patent, to which Appellant refers, claims methods of forming microarrays. Microarray methods have patentable utility as a research tool, just like a scale or a gas chromatograph. However, what the research tool measures does not necessarily have patentable utility, such as the object being weighed by the scale, or the compound being analyzed by the gas chromatograph. Such is the situation at issue.

The arguments and evidence merely show that microarray technology is important and useful to the scientific community. The publications referred to by Appellants do not show that the claimed invention has a patentable utility. The use of the claimed uncharacterized polynucleotides in such studies would have provided no more information than the use of any other orphan polynucleotide. The asserted utility for the claimed polynucleotide is not specific to the claimed polynucleotide. Due to the lack of disclosure of a correlation between the claimed polynucleotides and a particular disorder, the asserted utility is also not substantial, as discussed above.

B. The use of nucleic acids coding for proteins expressed by humans as tools for toxicology testing, drug discovery, and the diagnosis of disease is alleged as "well-established":

Beginning at p. 14 of the Brief, Appellants argue that the claimed polynucleotides are useful as tools for toxicology testing, drug discovery, and the diagnosis of disease and that these uses are "well-established". Each of these uses will be addressed

individually, because the facts and issues directed to each use are distinct and separable.

First, Appellants argue that toxicology testing is a well-established utility and concludes that the claimed polynucleotides could be used in this manner and that the claimed invention possesses utility. Appellants refer to other publications that discuss microarrays and gene expression technology with respect to drug screening/metabolism and toxicology testing at pp. 14-15 of the Brief. In addition, Appellants have cited Nuwaysir et al. reference (Molecular Carcinogenesis 1999, 24: 153-159), which describes the use of microarrays containing several classes of genes in the use of toxicology testing. Steiner and Anderson (Toxicology Letters 2000, 112-113: 467-471) describe expression profiling in toxicology. Also, Rockett and Dix (Environ. Health Perspec. 1999, 107: 681-685), which describe "Arrays are at their most powerful when they contain the entire genome of the species they are being used to study."

However, for a utility to be "well-established" it must be specific, substantial and credible. In this case, as indicated at page 14 of the Brief, all nucleic acids and genes are in some combination useful in toxicology testing. However, the particulars of toxicology testing with the claimed polynucleotides are not disclosed in the instant specification. The arguments and evidence provided by Appellants merely show that microarray technology is important and useful to the scientific community. For example, Rockett et al. paper (Xenobiotica 1999, 29(7): 655-691), states "Toxicology testing is now standard practice in the pharmaceutical industry." However, neither the toxic substances nor the susceptible organ systems (genes) are identified. This is, again, a

general utility for microassays that does not endow any particular polynucleotide with a specific and substantial utility. Because of this, such a utility is not specific and does not constitute a "well-established" utility. There is no doubt that cDNA microarray technology is an extremely valuable technique in gene expression monitoring, toxicology testing, and drug efficacy testing. However, the claims are not drawn to the technique. The claims of the instant invention are directed to polynucleotides, which have not been disclosed as being associated with any particular disease or condition by it being expressed at an altered level or form in diseased tissue as compared to the corresponding healthy tissue. Further, because any potential diagnostic utility is not yet known and has not yet been disclosed, the utility is not substantial. In addition, it is also not currently available in practical form. Moreover, use of the claimed polynucleotide in an array for toxicology screening is only useful in the sense that the information that is gained from the array is dependent on the pattern derived from the array, and says nothing with regard to each individual member of the array. Even if the expression of Appellants' individual polynucleotides are affected by a test compound in an array for drug screening, the specification does not disclose any specific and substantial interpretation for the result, and none is known in the art. Given this consideration, the individually claimed polynucleotides have no "well-established" use. The artisan is required to perform further experimentation on the claimed material itself in order to determine to what "use" any expression information regarding this nucleic acid could be put.

With regard to drug discovery and development, Appellants mention expression profiling as one use of the claimed polynucleotide. Appellants refer to recent developments as providing evidence that the benefits of this information are already beginning to manifest themselves. However, Appellants are incorrect in asserting that the efficacy (ability of producing a desired effect) of a compound could be evaluated from the result of a transcript image because there is no way to assess the meaning of any individual hit obtained from this procedure. The first requirement is that one must know the biological significance of the polynucleotide(s) which is(are) being evaluated. Without this information, the results of the transcript image are useless because one would not know if the polynucleotide expression should be increased or decreased or even what significance could be attributed to such changes in expression profiles.

With regard to diagnosis of disease, in order for a polynucleotide to be useful, as asserted, for diagnosis of a disease, there must be a well-established or disclosed correlation or relationship between the claimed polynucleotide and a disease or disorder. The presence of a polynucleotide in tissue that is derived from cancer cells is not sufficient for establishing a utility in diagnosis of disease in the absence of some information regarding a correlative or causal relationship between the expression of the claimed cDNA and the disease. If a molecule is to be used as a surrogate for a disease state, some disease state must be identified in some way with the molecule. There must be some expression pattern that would allow the claimed polynucleotide to be used in a diagnostic manner. Many proteins are expressed in normal tissues and diseased tissues. Therefore, one needs to know, e.g., that the claimed polynucleotide is either

present only in cancer tissue to the exclusion of normal tissue or is expressed in higher levels in diseased tissue compared to normal tissue (i.e. overexpression). Evidence of a differential expression might serve as a basis for use of the claimed polynucleotides as diagnostics for diseases. However, in the absence of any disclosed relationship between the claimed polynucleotides or the proteins that are encoded thereby and any disease or disorder and the lack of any correlation between the claimed polynucleotides or the encoded proteins with any known disease or disorder, any information obtained from an expression profile would only serve as the basis for further research on the observation itself. "Congress intended that no patent be granted on a chemical compound whose sole 'utility' consists of its potential role as an object of use-testing." *Brenner v. Manson*, 148 USPQ at 696. The disclosure does not present a substantial utility that would support the requirement of 35 U.S.C. §101.

C. Appellants' showing of facts overcomes the Examiner's concern that Appellants' invention lacks "specific utility":

At pages 25 and 26 of the brief, Appellants assert that the utility of claimed polynucleotides as gene specific probes depends upon specific properties of the polynucleotides, that is, their nucleic acid sequences. In addition, Appellants state that "the claimed polynucleotides can be used as highly specific probes in, for example, cDNA microarrays", and that "Given the fact that the claimed polynucleotides are known to be expressed, their utility as a measuring and analyzing instrument for expression levels is as indisputable as a scale's utility for measuring weight." Appellants further assert that while it is true that all polynucleotides expressed in humans have utility in

toxicology testing based on the property of being expressed at some time in the development or in the cell life cycle, this basis for utility does not preclude that utility from being specific and substantial. Appellants also assert that toxicology test using any particular expressed polypeptide or polynucleotide is dependent on the identity of that polypeptide or polynucleotide, not on its biological function or its disease association. Further, it is asserted that no two human expressed polypeptides or polynucleotides are interchangeable for toxicology testing because the effects on the expression of any two such polypeptides or polynucleotides will differ depending on the identity of the compound tested and the identities of the two polypeptides or polynucleotides.

As indicated above Appellants' submissions of additional facts after final have not been considered. Appellants' arguments have been fully considered but are not deemed be persuasive. First, the Examiner notes that the term "highly specific" in this context indicates that the hybridization would be highly specific, that is, that the sequence could be used to detect an exactly identical sequence. However, that is not the same thing as "specific" in the context of establishing utility; *any* sequence, regardless of origin or function, can be used in such a "highly specific" manner to detect a matching sequence; however, this is the very definition of a non-specific utility. Again, Appellants' analogy to a scale is inaccurate. Using the analogy to a scale, the Examiner would argue that it is the microarray that is analogous to a scale, as a scale may be used to measure the mass of any desired object, and a microarray may be used to detect the presence of any desired nucleic acid sequence. However, the fact that a scale is useful does not confer utility on any and all objects that might be weighed using

that scale, and the fact that the microarray may have utility does not confer utility on any and all nucleic acids that might be measured using the microarray. It remains that Appellants have disclosed no features or characteristics of the claimed nucleotides encoding SEQ ID NO: 22 or nucleotides of SEQ ID NO: 101 that would inform the experimenter as to what the significance of detecting that particular sequence would be. As stated above, detection of nucleotides encoding SEQ ID NO: 22 or nucleotides of SEQ ID NO: 101 under specific conditions using the claimed microarray would merely be an invitation to experiment further to determine what that result means, e.g. what significance the result has. Such an invitation to further experimentation does not meet the utility standard of 35 U.S.C. § 101. Since Appellants have not identified the expressed polypeptide or the polynucleotide that would confer utility that is specific and substantial the only means of showing "patentable" use is the demonstration of biological functions and potential disease conditions associated with the polynucleotides of the instant invention. That the effects of an agent on the expression of different genes may differ does not confer "specific" in the context of establishing utility; any sequence, regardless of origin or function, can be used in such a manner to for toxicology testing detect a matching sequence; however, this is the very definition of a non-specific utility. Therefore, Appellants' current invention would require substantial further research to identify a "specific" utility.

D. The Rockett and Lashkari references demonstrate that use of the claimed polynucleotide in expression profiling does not merely constitute further research on the claimed polynucleotides themselves:

Beginning on page 27, Appellants briefly note the previously discussed literature review. Appellants assert that the Rockett et al. paper (Xenobiotica 1999, 29(7): 655-691) confirms that the claimed invention is useful for differential expression analysis regardless of how the expression is regulated. Rockett et al. teach, "In the field of chemical induced toxicity, it is now becoming increasingly obvious that most adverse reactions to drugs and chemicals are the result of multiple gene regulation, some of which are causal and some of which are causally-related to the toxicological phenomenon *per se*. This observation has led to an up surge in interest in gene-profiling technologies which differentiate between the control and toxin-treated gene pools in target tissues and is therefore, of value in rationalizing the molecule mechanisms of xenobiotic-induced toxicity" (Rockett et al., page 656). Rockett et al. thus teach that microchip analyses are useful for the "identification and characterization of xenobiotics of unknown biological properties," in addition to those uses in "deciphering of molecular pathways and facilitating the development of new experimental and diagnostic procedures. Further, Appellants assert that the Office adopts a narrow reading of Lashkari et al. reference. Appellants note that the reference teaches the broader use of cDNA microarrays and in the analysis of numerous genes under many conditions. In summarizing the teaching of the Lashkari et al. reference Appellants assert that it teaches the whole genome analysis by cDNA microarrays and in the determination of the effect of environmental changes on gene regulatory networks and the roles of all gene products.

As argued previously in the Office Action mailed November 3, 2003, (pages: 8-10), in essence, Rockett is teaching that the purpose of such "open" microarrays, wherein the function of the specific nucleic acids is unknown, as is the case for nucleotides encoding SEQ ID NO: 22 or nucleotides of SEQ ID NO: 101, is that the results of the experiment are to be used to decipher molecular pathways, and facilitate the development of other experimental or diagnostic procedures. Such clearly falls under the category of use for further experimentation to determine the properties of that which is being claimed, in this case the further experimentation being to develop other procedures that would take advantage of the knowledge gained by the initial experiment, or to 'decipher' molecular pathways. Thus, it is clear from Rockett et al. that, that the use of the claimed polynucleotides in either microarrays or in gene expression monitoring merely constitutes further research to determine the significance of the claimed nucleic acid itself; if the results of such experiments demonstrated that the claimed sequences were or were not present under particular conditions, such would be an invitation to experiment to determine why, which would fall under the aegis of further experimentation to determine the properties of that which is being claimed.

Similarly, the Lashkari et al. publication, by Appellants' admission a pre-filing date reference that has not been previously cited, does not support Appellants' assertions: While Lashkari et al. indeed teach that "amplicons", or portions of DNA amplified from the genome by PCR can be used by arraying onto glass for expression analysis, the very first paragraph of the paper states "This massive and increasing amount of sequence information allows the development of novel experimental

approaches to identify gene function." The paragraph bridging the columns of that page starts "Experimental analysis must be performed to thoroughly understand the biological function of a gene product." The same paragraph states "it is clear that novel strategies are necessary to efficiently pursue the next phase of genome projects- whole-genome experimental analysis to explore gene expression, gene product function, and other genome functions (emphasis added)." Thus, Lashkari et al. are clearly teaching that sequences of unknown function or significance are used in such strategies *to* learn more about the sequences themselves and the genes they represent. Thus, the examiner maintains that this is clearly further research of the type that is not sanctioned as fulfilling the requirements of 35 U.S.C. § 101. As argued above, there is no doubt that cDNA microarray technology is an extremely valuable technique in gene expression monitoring, toxicology testing, and drug efficacy testing. However, the claims are not drawn to the technique. The claims are directed to polynucleotides, which have not been disclosed as being associated with any particular disease or condition by its being expressed at an altered level or form in diseased tissue as compared to the corresponding healthy tissue. Any such polynucleotide could be added to a microarray. Thus, this asserted utility is not specific. Determining the relationship between the claimed polynucleotides and any specific disease or disorder would require significant further research.

E. Use of the claimed polynucleotides in toxicology testing:

Appellants argue that the Office is substituting its own judgment for that of the Appellants' own expert. In addition, at the bottom of p. 32 of the Brief, Appellants argue

that the examiner does not address the fact that, as described on p. 55 of the specification, the claimed polynucleotide can be used as highly specific probes to measure both the existence and amount of complementary mRNA sequences known to be expression products of the claimed polynucleotides. Appellant concludes that the claimed invention is not, in that regard, some random sequence whose value, as a probe is speculative or would require further research to determine. Appellants also assert that monitoring the expression of the SEQ ID NO: 22 encoding polynucleotides is a method of testing the toxicology of drug candidates during the drug development process. Appellants refer to other publications that discuss microarrays and gene expression technology with respect to drug screening/metabolism and toxicology testing at pp. 14-15 of the Brief. It is also asserted Dr. Bedilion states that "good drugs are not only potent, they are specific. It is also stated that they have strong effects on a specific biological target and minimal effects on all other biological targets." Further, the Appellants assert that, if the expression of a particular polynucleotide is affected in any way by the exposure to a test compound, and if that particular polynucleotide is not the specific target of the test compound (e.g., if the test compound is a drug candidate), then the change in expression is an indication that the test compound has undesirable toxic side effects. It is further suggested that such an indication of possible toxicity is specific not only for each compound tested, but also for each and every individual polynucleotide whose expression is being monitored. Appellants further assert that, the Examiner continues to view the utility in toxicology testing of the claimed polynucleotides as requiring knowledge of either the biological function or disease

association of the claimed polynucleotides. In addition it is asserted that the Examiner views toxicology testing as a process to measure the toxicity of a drug candidate only when that drug candidate is specifically targeted to the claimed polynucleotides. Further, it is asserted that the Examiner has refused to consider that the claimed polynucleotides are useful for measuring the toxicity of drug candidates which are targeted not to the claimed polynucleotides, but to other polynucleotides and the utility of the claimed polynucleotides does not require any knowledge of the biological function or disease association of the SEQ ID NO: 22 polypeptide or SEQ ID N0: 101 polynucleotide and is a specific, substantial and credible utility.

Contrary to Appellants assertion that the Office is substituting its own judgment for that of Appellants' own expert, the examiner merely pointed that the declaration of filed by Dr. Tod Bedilion under 37 C.F.R. § 1.132 on 6/26/03 is insufficient to overcome the rejection of claims 23-29 and 31 because the instant specification provides general methods and no specific examples. Further, with respect to Appellants assertion that the "Examiner must accept the Appellants' assertion to be true", Appellants' credibility has not been challenged. The examiner only determines if the assertions are able to overcome the rejection of record. Dr. Tod Bedilion's references to establishment of utility point to the practice of microarray technology as proposed and as addressed above. Although it is claimed that the nucleotides encoding SEQ ID NO: 22 or nucleotides of SEQ ID NO: 101 can be used as probe for microarray, there is no demonstration of the use of specific SEQ IDs for the purpose of detecting differential expression and in the use for diagnosis is provided.

Any polynucleotide is a highly specific probe for itself or its complement, or any mRNA that can be transcribed from it. Such can be said for any polynucleotide and it reveals nothing about the function of the polynucleotide itself. Thus, this asserted utility is not substantial.

The particulars of toxicology testing with the claimed polynucleotides are not disclosed in the instant specification. Since neither the toxic substances nor the susceptible polynucleotide sequence has been identified, this utility could virtually apply to every member of a general class of materials, such as any collection of proteins or DNA, but is only potential with respect to the claimed polynucleotides.

Since the artisan would be required to perform further experimentation on the claimed material itself in order to determine what "use" any expression information regarding this nucleic acid or protein could be put, the asserted utility is not specific and substantial. For the reasons stated above, utility in a general assay is not specific to any polynucleotide and, since there is no utility disclosed for detecting this particular polynucleotide, specific detection of HTMPN-22 is not a substantial utility. The invention therefore lacks a specific and substantial utility.

F. The similarity of the polypeptide encoded by the claimed invention to another polypeptide of undisputed utility is asserted to demonstrate utility:

At p. 33 of the Brief, Appellants argues that the utility of the claimed polynucleotide can be imputed based on the relationship between the polypeptide it encodes, HTMPN-22, and another polypeptide of unquestioned utility, Ring3. Appellants also assert that two polypeptides have sufficient similarities in their sequences that a

person of ordinary skill in the art would recognize with more than a reasonable probability that the polypeptide encoded for by the claimed invention has utility similar to Ring3. It is stated by the Appellants that the BLAST search demonstrated that HTMPN-22 has 57% homology over 548 amino acid residues to mouse Ring3, a nuclear serine-threonine kinase. Thus, based on this homology Appellants assert that HTMPN-22 is a Ring3 homolog. Further, it is asserted that HTMPN-22 contains a bromodomain, a domain found in various transcriptional regulators, from residues A80-N140.

In addition, on page 34 of the Brief, Appellant discusses the Ostrowski et al. (1998) reference. This article was published before the priority date of the instant Application. This pre filing reference discusses the "Stimulation of p85/RING3 kinase in multiple organs after systemic administration of mitogens into mice". The authors conclude that the activation of p85/RING3 kinase by growth factors in multiple organs might reflect involvement of this enzyme in the pathogenesis of leukemias and other proliferative diseases. Appellants also assert that based on the northern analysis of SEQ ID NO: 101 predominant expression is observed in cDNA libraries associated with cancer, inflammation and the immune response and fetal development. Thus it is argued by the Appellants that one of skill in the art would have understood at the time of filing that polynucleotides encoding HTMPN-22 would be expected to have utility in the diagnosis of cancers as described in the specification. Appellants argue that it is undisputed that the polypeptide encoded for by the claimed polynucleotide shares more than 57% homology over 548 amino acid residues to mouse Ring3, a nuclear serine-threonine kinase. Further, it is asserted that HTMPN-22 contains a bromodomain, a

domain found in various transcriptional regulators, from residues A80-N140. It is also asserted that this is more than enough homology to demonstrate a reasonable probability that the utility of Ring3 can be imputed to the claimed invention through the polypeptide it encodes. Appellant refers to Brenner (1998, PNAS USA 95:6073-6078) as evidence that the probability that two unrelated polypeptides share more than 40% sequence homology over 70 amino acid residues is exceedingly small. Appellant urges that the examiner must accept that the homology demonstrates utility unless evidence or sound scientific reasoning is brought forth that a person of ordinary skill in the art would doubt utility. Appellant criticizes the literature cited by the Examiner as disclosing some of the difficulties that may be involved in predicting protein function, since none suggests that functional homology can be inferred by a reasonable probability in this case. As noted by the Appellants', the homology between pendrin and DRA is lower than that between HTMPN-22 and mouse RING3 (45% vs. 57%). Appellants conclude based on the higher homology present between HTMPN-22 and RING3, one of ordinary skilled in the art would be reasonably be convinced (more likely than not) that HTMPN-22 is indeed a member of the RING3 related family of proteins.

Appellant's arguments have been fully considered but have not been found to be persuasive. Ostrowski do not teach a substantial utility because Ostrowski et al. are only speculating on the possible involvement of this kinase in the pathogenesis of leukemias and other proliferative diseases. For example, Ostrowski et al., conclude that "results of these studies may reflect involvement of p85/RING3 kinase in diseases where abnormal cell proliferation is responsible for the pathological process" which is

"consistent with the observation that the activity of this enzyme is very high in leukocytes from patients with acute and chronic leukemias" (Ostrowski et al., page 1227, col. 1). Even if Ostrowski et al. had shown a correlation with the activity levels of this enzyme/protein (p85/RING3) and patients with leukemias or immune disorders there is no evidence to indicate that the HTMPN-22 protein is identical to p85/RING3 kinase protein or to indicate a relationship between RING3 protein of Ostrowski et al. and HTMPN-22. Although a sequence homologous to 'RING3' motif is found in the HTMPN-22 protein of the instant invention there is no evidence to indicate that p85/RING3 kinase described by Ostrowski et al. is identical. In fact, Appellants have indicated that the claimed polynucleotide shares only about 57% homology over 548 amino acid residues out of the 688 amino acids to mouse Ring3 kinase (see Brief p. 35). In addition, there is no evidence in the art that would indicate that proteins with 57% homology would have identical functional activities. This limited structural similarity is not indicative or predictive of functional similarity and thus does not provide a well-established utility for the instant polynucleotide. Further, there is no evidence to indicate that 'RING3' motif will alone cause the increased activity of these proteins in patients with leukemia. In addition, Appellants have failed to demonstrate that HTMPN-22 has the same functional properties that are similar to p85/RING3 kinase protein. Therefore,the limited similarity based on the homology of mouse Ring3 protein and HTMPN-22 of the instant invention does not provide the HTMPN-22 with a specific and substantial or a well-established utility.

With respect to Appellants' assertion of a diagnostic utility, there is no correlation to show the message levels or the size of HTMPN-22 in normal individuals and patients. The specification does not disclose the results of the required control in order to draw any conclusions regarding disease, namely, that the claimed polynucleotide is not expressed (or is expressed at an altered level or form) in the corresponding healthy tissues. Many genes expressed in diseased tissues have nothing whatsoever to do with the disease and are not targets for drug development or toxicology. For example, actin and histone genes are expressed in diseased tissues as well; they are constitutively expressed in all tissues. Therefore,further research would be required to establish a utility in cancer detection for the disclosed polynucleotide.

The assertion that the disclosed Ring3 protein have biological activities similar to known Ring3 –related bromodomain protein is not sufficient to establish a utility in the absence of evidence. While a general effect on cell proliferation may be suggested, there is a great diversity of cell types affected by these polypeptides. The specification does not disclose which cell types are responsive to the polypeptides encoded by the claimed polynucleotides or in what way they are responsive. Significant further research would be required of the skilled artisan to determine which cells are responsive, and in what way, and thus the asserted utility is not substantial. Similarly, mere expression in a cancer cell does not mean that the polynucleotide is an appropriate target for drug development or toxicology testing. Cancer cells express many polynucleotides, such as constitutively expressed polynucleotides, which are not appropriate targets. The specification has not disclosed a specific disease or disorder

of any type wherein the claimed polynucleotides are expressed at altered amounts or forms relative to the required control healthy tissue. Significant further research would be required of the skilled artisan to identify such a disease or disorder. Therefore the asserted utility is not substantial.

Further, as previously indicated in the Office Action of 3/25/2003, Scott et al. (1999) teaches that the homology of a polypeptide is not *in fact* a reliable indicator of the functional characteristics. In this reference, on the basis of homology and the presence of a slightly modified sulfate-transporter signature sequence comprising its putative second transmembrane domain it was predicted that the pendrin protein to function as a sulfate transporter. However, experimental results indicated that it was a chloride and iodide transporter. Therefore, the rejection sets forth that, among related polypeptides, structural similarity is not predictive of functional similarity. Even higher degree of sequence identity between members of gene family is not predictive of functional similarity. Appellants' current proposal would require substantial further research to identify a utility.

Appellants cite the post-filing reference of French et al. (2001) as showing that HTMPN-22 has 96% amino acid sequence identity to the short form of human BRD4. This is a reference that was previously cited in 3/25/2003 as an art of interest by the Examiner (not prior art because of the priority date), discloses that that rearrangements of the BRD4 gene is responsible for an aggressive pediatric carcinoma. In addition, Appellants also cites a post filing reference of Maruyama et al. (2002). This reference discloses that Brd4 is a member of the BET family of bromodomain proteins that

includes RING3, Brd2 and that Brd4 regulates cell cycle progression. Thus, the Appellants assert that these post-filing references confirm the identification of HTMPN-22 as a RING3 related protein and also confirm the association of this sequence with cancers. It is asserted that one of skill in the art would clearly understand that the claimed sequences encoding HTMPN-22, as well as the claimed 90% variants of these sequences, would have utility in the diagnosis of cancers. Beginning at p. 37 of the Brief, Appellants argue that the association of RING3 with leukemia is not at all speculative, but a matter of fact. Further, the Appellants assert that although, the particular biological function of RING3 in causing the disease may not be known, but the correlation of activity levels of RING3 with leukemia is a well-known fact. Furthermore, Appellants quotes the Office "the mere correlation of the presence of the nucleic acid, in a manner that would be found to be credible by a person of ordinary skill in the art, with the presence of a disease or condition would clearly meet the requirements of 35 U.S.C. § 101" and indicates that the RING3 activity in leukemia described by Ostrowski et al. is such a correlation.

Contrary to Appellants' assertion, the specification as originally filed does not specifically recite that HTMPN-22 is specifically involved neither in cancer nor in the diagnosis of this disease. Application as filed alleges several general utilities that cannot fulfill the utility requirement under 35 USC 101 because they are general and not specific (see page 23, lines 26-30 and page 37, line 25 to page 40, line 12). Therefore, one of skill in the art would not clearly understand that the claimed sequences encoding

HTMPN-22, as well as the claimed 90% variants of these sequences, would have utility in the diagnosis of cancer.

Appellants provide no evidence to substantiate the stated correlation of Ring3 actiivty with leukemia nor do they *disclose* any association of HTMPN-22 and leukemia. While there are many families of polypeptides that are well conserved both structurally and functionally, including most enzymes and "housekeeping" polypeptides such as myosins, actins and globins, the art recognizes that structural similarity among cytokines and receptors is not predictive of functional similarity. Regardless of Ostrowski et al.'s teachings there is no evidence provided by the Appellants to indicate that Ostrowski et al. protein and the HTMPN-22 protein are identical and thus *that HTMPN-22 is correlated with disease.* The association of Ring3 with leukemia predicts no similar association for HTMPN-22. There is no teaching that the proteins are identical in either function or expression. At the bottom of p.37 of the Brief Appellants argues that the Examiner has missed the point, "the fact that HTMPN-22 is a member of the Ring3 family demonstrates utility because all the members of this particular family have utility for the diagnosis of cell proliferative disorders." In fact the examiner noted that the SEQ ID NO: 101 of the instant invention has 99.2% sequence homology to BRD4 nucleotide sequence described by post filing French et al (2001) reference. In addition, French et al. also shows that HTMPN-22 has 96% amino acid sequence identity to the short form of human BRD4, which is responsible for an aggressive pediatric carcinoma. Further, Appellants also cite a post filing reference of Maruyama et al. (2002). This reference discloses that Brd4 is a member of the BET family of

bromodomain proteins that includes RING3, Brd2 and that Brd4 regulates cell cycle progression. Thus, the Appellants assert that these post-filing references confirm the identification of HTMPN-22 as a RING3 related protein and also confirm the association of this sequence with cancers. Appellants further argue that, one of skilled in the art would readily understand, based upon the disclosure in the specification identifying HTMPN-22 as a RING3 related protein and that HTMPN-22 would be associated with cancer and therefore useful in the diagnosis of cancer. On p.38 of the Brief, Appellants assert that based on the cDNA library analysis of SEQ ID NO: 101, expression is predominantly found associated with cancer, inflammation and the immune response, and fetal development. Appellants further assert that based on the cDNA analysis and the isolation of polynucleotides encoding SEQ ID NO: 22 from a brain tumor library, one of skill in the art would have understood at the time of filing that polynucleotides encoding HTMPN-22 would be expected to have utility in the diagnosis of cancers, as described in the specification.

Contrary to Appellants' assertion, the specification as originally filed does not specifically recite that HTMPN-22 is specifically involved either in cancer or in the diagnosis of this disease. As discussed previously in the Office Action of 11/03/2003, Application as filed alleges several general utilities that cannot fulfill the utility requirement under 35 USC 101 because they are general and not specific (see page 23, lines 26-30 and page 37, line 25 to page 40, line 12). At the time of filing of the instant application Appellants had only identified HTMPN-22 to be a 'Ring3' motif containing polypeptide (Table. 2) possibly involved in the diagnosis and treatment of a

plethora of diseases; all of the potential uses in the disclosure are merely prophetic. There was no disclosure in the specification to indicate nucleotides encoding HTMPN-22 can be used in the diagnosis of cancer. It is the post filing references of French et al. and Maruyama et al., that identified HTMPN-22 as RING3 related bromodomain protein and that it was associated with cancer, therefore useful in the diagnosis of cancer. Thus, one of skill in the art would not have readily understood, based upon the disclosure in the specification the association of HTMPN-22 in cancer and the diagnosis of cancer at the time of filing.

Appellants have not provided any evidence that would indicate that nucleotides encoding the polynucleotide of SEQ ID NO: 22 or polynucleotides of SEQ ID NO: 101 are differentially expressed in tissues that would indicate that these sequences are associated with cancer, inflammation and the immune response and fetal development. Although the specification (Table. 3) claims that the polynucleotide is differentially expressed in the disease tissue, the specification does not teach what is the normal level of expression, does not indicate how high the expression level is compared to for example, normal tissue; and does not provide a statistical correlation to the level of expression (for example, there is no indication of how many samples were compared to study the expression). In addition, the specification does not disclose a correlation between any specific disorder and the altered levels or form of the claimed polypeptides. Also, the specification does not teach or describe the function of this yet to be identified polypeptide. However, in the absence of any disclosed relationship between the claimed polynucleotide or the protein that is encoded thereby and any

disease or disorder, any information obtained from an expression profile would only serve as the basis for further research on the observation itself.

Contrary to Appellants assertion, isolating the polynucleotides encoding SEQ ID NO: 22 from a brain tumor library does not mean that, one of skill in the art would have understood at the time of filing that polynucleotides encoding HTMPN-22 would be expected to have utility in the diagnosis of cancers because the disclosure does not provide any correlation or biological significance of HTMPN-22 and brain tumors. With regard to diagnosis of disease, in order for a polynucleotide to be useful, as asserted, for diagnosis of a disease, there must be a well-established or disclosed correlation or relationship between the claimed polynucleotide and a disease or disorder. The presence of a polynucleotide in tissue that is derived from cancer cells is not sufficient for establishing a utility in diagnosis of disease in the absence of some information regarding a correlative or causal relationship between the expression of the claimed cDNA and the disease. If a molecule is to be used as a surrogate for a disease state, some disease state must be identified in some way with the molecule. There must be some expression pattern that would allow the claimed polynucleotide to be used in a diagnostic manner. Many proteins are expressed in normal tissues and diseased tissues. Therefore, one needs to know, e.g., that the claimed polynucleotide is either present only in cancer tissue to the exclusion of normal tissue or is expressed in higher levels in diseased tissue compared to normal tissue (i.e. overexpression). Evidence of a differential expression might serve as a basis for use of the claimed polynucleotides as diagnostics for diseases. However, in the absence of any disclosed relationship

between the claimed polynucleotides or the proteins that are encoded thereby and any disease or disorder and the lack of any correlation between the claimed polynucleotides or the encoded proteins with any known disease or disorder, any information obtained from an expression profile would only serve as the basis for further research on the observation itself. "Congress intended that no patent be granted on a chemical compound whose sole 'utility' consists of its potential role as an object of use-testing." *Brenner v. Manson*, 148 USPQ at 696. The disclosure does not present a substantial utility that would support the requirement of 35 U.S.C. §101.

G. The asserted utility in toxicology testing and expression profiling also applies to the claimed polynucleotide variants:

The examiner notes that even if the claimed polynucleotides in toxicology testing and expression profiling were to be considered to be sufficient to meet the utility requirement under 35 U.S.C. § 101, the scope of the claims would not be commensurate with such use, as such use would apply only to the exact, naturally occurring sequence, to nucleic acids which vary from such by codon degeneracy (have different sequence, but encode the same protein) and not to nucleic acids 90% identical to the specifically disclosed sequence.

H. Objective evidence is alleged to corroborate the utilities of the claimed invention:

Beginning at p. 39 of the Brief, Appellants argue that a "real-world" utility exists if actual use or commercial success can be shown. Citing case law, Appellants urges that such a showing is conclusive proof of utility. Appellants argue that a vibrant market has

developed for databases containing all expressed genes, including those of Incyte, the real party at interest in the instant appeal. Appellants urge that Incyte's customers and the scientific community have acknowledged that Incyte's databases have proven valuable, and that the databases including the claimed polynucleotide would be even more valuable.

Appellants' arguments have been fully considered but are not deemed to be persuasive. The case law indicates that a rejection under 35 U.S.C. § 101 *for lack of operability* can be overcome by a showing of actual use or commercial success. The instant issue is whether or not the asserted utilities meet the three-pronged test for credibility, specificity, and substantiality. Such is not necessarily addressed by a showing of commercial success or actual use. As argued previously, many products that lack patentable utility enjoy commercial success, are actually used, and are considered valuable. These include silly fads such as pet rocks, but also include serious scientific products like orphan receptors. Furthermore, what is marketed is a database, not a single gene with no known function.

III. The patent examiner's rejections are alleged as being without merit.

A. The precise biological role or function of an expressed polynucleotide is alleged as being not required to demonstrate utility:

Beginning at p. 41 of the Brief, Appellants characterize the examiner's rejection as being based on the grounds that, without information as to the precise biological role of the claimed invention, the claimed invention lacks specific patentable utility.

Appellants characterize the examiner's position as it is not enough that a person skilled in the art could use and would want to use the claimed invention either by itself or in a microarray, but that Appellants also is required to provide a specific and substantial interpretation of the results generated in a given expression analysis. Appellants argue that specific and substantial interpretations regarding biological function may be required by technical journals, but are not necessary for patents. Appellants urge that the relevant question is not how or why the invention works, but whether the invention provides an identifiable benefit. Appellants argue that the present invention meets this test. Appellants argue that the threshold for patentable utility is low. Furthermore, it is argued that only throwaway utilities are insufficient, and that knowledge of biological function is not required.

This is not found to be persuasive, as it mischaracterizes the examiner's position. The rejection never states that the precise biological role of a polynucleotide is required for it to possess patentable utility. If a polynucleotide is disclosed as being differentially expressed in a disease or disorder, even if nothing is known or hypothesized about the activities of the encoded polypeptide, then the polynucleotide has patentable utility as a disease marker and in the toxicology/drug screening microarray assays discussed at length by Appellants. However, if a specification does not disclose such information, as is the case here, then there is no patentable utility. If a compound causes the claimed polynucleotide to be expressed at a decreased level in a microarray, does that mean the compound is a potential drug or a potential toxin? That determination requires significant further research, and thus the asserted utility is not substantial. Also, any

expressed polynucleotide *can* be used in a microarray; thus the unasserted utility is also not specific.

B. Because the uses of polynucleotides encoding HTMPN-22 in toxicology testing, drug discovery, and disease diagnosis are asserted as practical uses beyond mere study of the invention itself, the claimed invention has substantial utility.

At p. 43 of the Brief, Appellants argue that the rejection is incorrectly based on the grounds that the use of an invention as a tool for research is not a substantial use. Appellants urge that only a limited subset of research uses are not substantial: those in which the only known use for the claimed invention is to be an object of further study, thus merely inviting further research.

This is not found to be persuasive. As discussed above, whereas a scale or a microarray or a gas chromatograph has patentable utility as a research tool, the objects being evaluated with those research tools do not necessarily have patentable utility. In the instant case, the claimed polynucleotide is not disclosed as having a specific activity, or having any property (such as a differential pattern of expression in diseased tissue) that can be specifically useful. The claimed invention is, in fact, the object of further study, merely inviting further research. None of the utilities asserted for the claimed polynucleotide meets the three-pronged test of being specific, substantial and credible.

IV. By requiring the patent applicant to assert a particular or unique utility, it is alleged that the patent examination utility guidelines and training materials applied by the patent examiner misstate the law.

Beginning at p. 43 of the Brief, Appellant challenges the legality of the Patent Examination Utility Guidelines.

Since a Primary Examiner has no authority to comment on the legality of the Guidelines, this issue will be reserved for ruling by the Board of Patent Appeals and Interferences.

V. To the extent the rejection of the invention under 35 U.S.C. § 112, first paragraph, is based on the alleged improper rejection for lack of utility under 35 U.S.C. § 101, it is alleged that the rejection must be reversed

As Appellants indicate at p. 45 of the Response, a rejection under § 112, first paragraph, may be affirmed on the same basis as a lack of utility rejection under § 101. *See, e.g., In re Swartz*, 56 USPQ2d 1703 (Fed. Cir. 2000); *In re Kirk*, 153 USPQ 48 (CCPA 1967).

Therefore, for reasons set forth above, Appellants arguments and exhibits have been fully and carefully considered, but are not considered sufficient to rebut the prima facie case of lack of utility and it is believed that the rejections should be sustained.

ISSUE THREE : Enablement rejections under 35 U.S. C § 112, first paragraph of the recited variant polynucleotides and polynucleotides encoding polypeptide variants and fragments:

Appellants at p.46 of the Brief, note that the claims are drawn to polynucleotides and not proteins; thus it is the functionality of the claimed polynucleotides, not the proteins encoded by such is relevant. Further, it is asserted that members of the claimed genus of variants may be useful even if they encode proteins that lack activity. Further, with respect to the claimed biologically active fragments, Appellant asserts that the Examiner is incorrect in stating that that there is no activity ascribed to A80-N140 fragment. Appellants at the bottom of p.47 of the Brief, state that based on the guidance provided in the specification, one of ordinary skill in the art would be able to make and use immunogenic fragments of SEQ ID NO: 22 (or polynucleotides encoding these fragments) without any undue experimentation. Further, it is asserted that the antibodies can be used in the diagnostic methods described in the specification.

Although Appellants assert that the specification discloses further ways to use the claimed polynucleotide variants, including as associated with disease states, there is no such evidence disclosed in specification.

While it is true that the specification on page 79 described A80-N140 as a Ring3 sequence, there is no disclosure to indicate that A80-N140 corresponds to art described bromodomain sequence. In addition, the disclosure does not teach that SEQ ID NO: 22 or A80-N140 sequence has any particular biological activity. Only the post filing disclosures of French et al. and Marayuma et al. describe the "bromodomain" motif that

is known to interact with chromatin molecules. Thus, in the absence of a description that indicates that A80-N140 fragment is identical to the art described bromodomain region, additional experimentation would be required to identify the chromatin-targeting region of HTMPN-22. In addition, there is no disclosure in the specification that would indicate that any antibodies generated towards polypeptide of SEQ ID NO: 22 can be used to diagnose diseases. Furthermore, since any 6 amino acids can be antigenic, in the absence of further guidance, it would require an artisan to use the current invention as a starting point for further experimentation to generate antibodies that could be used to diagnose a specific diseases.

ISSUE FOUR : Written description rejections under 35 U.S. C § 112, first paragraph:

The specification provides an adequate written description of the claimed "variants" and "fragments" of SEQ ID NO: 22 and SEQ ID NO: 101.

At page 49 of the Brief, Appellants argue that on pages 11 and 12 of the specification they have recited the variants having 90% sequence identity to polynucleotide encoding SEQ ID NO: 22 or nucleotide of SEQ ID NO: 101 and allege that one of ordinary skill in the art would recognize naturally-occurring variants of SEQ ID NO: 101 having 90% sequence identity to SEQ ID NO: 101 or encoding amino acid sequences having 90% identity to SEQ ID NO: 22. Furthermore, it is alleged that given SEQ ID NO: 22 and SEQ ID NO: 101, one of ordinary skill in the art would recognize naturally-occurring variants of SEQ ID NO: 101 having 90% sequence identity to SEQ

ID NO: 101 or encoding amino acid sequences having 90% identity to SEQ ID NO: 22. On page 50, Appellants argue that variants are described, for example, at pages 15 and 23 of the specification. At bridging pages 50-51, Appellants argue that "one of ordinary skill in the art would recognize naturally occurring variants of SEQ ID NO: 22 having 90% identity to SEQ ID NO: 22". Appellants' further argue that the sequence information is not provided in a vacuum. These arguments are not persuasive because Applicants have described only a single naturally occurring sequence, that of SEQ ID NO: 101, which encodes the predicted protein of SEQ ID NO: 22. Although, several sequences (SEQ ID NO's) have been provided there is no evidence that these sequences have at least 90% identity to nucleotides encoding SEQ ID NO: 22 or SEQ ID NO: 101. For example, there is no alignment provided that would indicate that the sequences have homology. In addition, no other naturally occurring sequences have been described as obtainable from either human, or any other animal. A breadth of 90% identity at the nucleic acid level would reasonably be expected to encompass homologues obtained from other primate species such as macaque, rhesus, gibbon, as well as from non-primate species, such as rat or mouse, giraffe, hippo, or even frog or yeast, depending upon the evolutionary conservation of the gene in question. Although Appellants assert that the specification on pages 73 and 97 provides clones and libraries from which HTMPN-22 clone was identified, there is no disclosure of the various fragments and variants contemplated in the instant invention. Appellants have provided no information or description about how conserved the gene in question is, that is, how similar the homologues from other species would be expected to be, nor have they described a

single species other than the single allele (instance) of the gene as obtained from a single human. There is no description about the function of the gene nor the protein encoded thereby, such as would allow one of skill in the art to predict what portions of the disclosed sequence would be expected to be conserved. Similarly, with respect to claims to nucleic acids encoding proteins with 90% identity, again, no such naturally occurring variants have been disclosed, nor has any function been described for the encoded protein, nor ways in which the encoded protein might be altered while retaining that function. Further in respect to this issue, it is a nucleic acid that is being claimed; without having a written description of all naturally occurring sequences within the metes and bounds of the claims, one would not be capable of determining whether or not a given species was claimed. In addition, the mere recitation of "naturally occurring" does not obviate the issue raised with respect to written description.

One could certainly determine whether a protein that one had obtained from nature were 90% identical to SEQ ID NO: 22, but that same person, handed a protein in a test tube, would have no way of determining whether that protein were 'naturally occurring'. The same applies to the nucleic acid of SEQ ID NO: 101. Page 15 of the specification merely defines what an allelic variant *is*. It does not describe even a single naturally occurring allelic variant. Similarly, at page 23, the specification merely describes some of the things that *may* happen to cause allelic variation, i.e. to give rise to 'naturally occurring' species within the scope of the claims. However, it is not true that one could find in nature any and all possible changes within a given gene, and the specification has described not a single naturally occurring variant of SEQ ID NO: 101.

Further, even *if* the specification had described some naturally occurring human allelic variants within the scope of the claims, such would not be commensurate in scope with the claims. This is because one of ordinary skill in the art would expect 10% variation at the nucleic acid level to read on species homologues, that is, similar sequences as isolated from different biological species. There is not a single sequence disclosed that is obtained from another biological species.

With respect to Appellants arguments regarding sequences encoding biologically and immunologically active fragments of SEQ ID NO: 22, the Appellants are correct in that specification discloses a specific signature sequence A80-N140 of SEQ ID NO: 22. In addition, the specification also discloses nucleotide encoding SEQ ID NO: 22, which includes sequence of SEQ ID NO: 101. However, the instant claims read on all nucleic acid molecules encoding a polypeptide that is consisting of a amino acid sequence which is at least 90% identical to the amino acid sequence of SEQ ID NO: 22 or a nucleic acid molecules encoding a polypeptide that is consisting of a amino acid sequence which is a biologically active fragment of the polypeptide sequence of SEQ ID NO: 22 or a nucleic acid molecules encoding a polypeptide that is consisting of a amino acid sequence which is an immunogenic fragment of the polypeptide sequence of SEQ ID NO: 22, which the specification as failed to disclose. Contrary to Appellants' assertion, there is no description of the immunogeneic epitopes such as regions at the C-terminus or hydrophilic regions of the instant invention described in the specification at page 70, lines 2-7. The specification only teaches general computer based methods to determine regions of high immunogenecity (page 70, lines 2-7). Therefore, lacking

adequate written description. Similarly, Appellants have indicated the fragments listed in Table 1 can be used for hybridization. However, it is the position of the Office that Appellants have not provided adequate written description for the various biological activities contemplated for all the fragments contemplated in the instant claims. In addition, it appears that the Appellants were not in possession of the various fragments contemplated.

A. The present claims specifically define the claimed genus through the recitation of chemical structure:

At page 51 of the Brief, Appellants argue that the situation in this case distinguishes from that in *Fiers* and *Lilly* because the nucleic acids in those cases were defined based on functional characteristics, and not, as here, based upon percentage identity.

This argument is not persuasive because as a practical matter, the claims in both those cases were limited to the naturally occurring sequences encoding particular proteins, which proteins are well known by their functions. In this case, Appellants claim requires no such conserved function. Given that, to take the claim from *Fiers* cited by Appellants, the person of ordinary skill in the art would immediately recognize that any and all species within the metes and bounds of "A DNA which consists essentially of a DNA which codes for a human fibroblast interferon-beta polypeptide" would encode proteins with *greater* than the 90% identity claimed by Appellants; the person of ordinary skill in the art would not expect to find that great amount of variation within a single species, while still meeting the functional limitation of being a human fibroblast

interferon-beta polypeptide. Thus, the claims in both *Lilly* and *Fiers* were of *narrower* scope than the claims in question here. However, similar to the case here, both *Lilly* and *Fiers* involved disclosures of only a single sequence. Accordingly, the parallels to the instant case are clear. Thus, while recitation of structure is indeed an important factor, mere recitation of structure (90% identity to nucleic acid or the protein encoded thereby) and a product-by-process type of limitation ("naturally occurring"), without even a limitation to the biological species from which the single disclosed nucleic acid of SEQ ID NO: 101 was obtained, is insufficient to meet the written description requirement.

B. The present claims do not define a genus, which is "highly variant":

At page 54 of the Brief, Appellants argue that the claims do not define a genus, which is "highly variant". Appellants further argue that the Brenner reference states that 30% identity is a reliable threshold for establishing evolutionary homology between two sequences aligned over at least 150 residues, and that the present invention is directed to polypeptides related to the amino acid sequence of SEQ ID NO: 22 and polynucleotides related to the nucleotide sequence of SEQ ID NO: 101.

Based on analysis of Brenner et al., Appellants extrapolate the variability threshold required for establishing evolutionary homology between two sequences aligned over at least 150 residues. Brenner et al. assess that 40% identity over at least 70 residues is reliable in signifying homology between proteins. Based on these evolutionary calculations, Appellants continue to assert that the variation of the instant 90% variants of instant SEQ ID NOs: 22 and 101 is far less than what Brenner et al. had envisioned for related proteins. These arguments are not persuasive, because

Brenner's calculations represent theoretical assessments and can form the basis of a hypothesis, however these calculations while providing evolutionary information do not establish the relationship of a protein biologically without a second criterion such as function, or location, or occurrence, or associated expression. Therefore, in the instant case, Brenner's calculations and Appellants' analogy are well accepted as two distinct facts, but do not apply to the current grounds of rejection of lack of written description of the claimed genus described only by the chemical structure of one member without a description of how that structure correlates with the definitive properties of the genus encompassed.

To elucidate further, the issue here is not whether or not sequences 90% identical to SEQ ID NO: 22 or 101 would be considered to be evolutionarily related to such, but whether or not the specification as originally filed provides an adequate written description of the 'genus'. While 90% identity is certainly sufficient to establish that two proteins are structurally similar and/or evolutionarily related, it is not predictive of function. Evolutionary relatedness merely means that two entities (proteins, nucleic acid sequences, or even whole organisms) are evolutionary descendants of a common ancestor. In the process of diverging, said proteins, nucleic acids or organisms take on different structures and functions. To follow Appellants' argument to the level of organisms, it would appear that Appellants would argue that the written description of a monkey constitutes an adequate written description of a human, as the two are well known to be over 90% identical. At the protein level, there are less extreme examples; VEGF (a member of the PDGF, or platelet-derived growth factor, family) is mitogenic for

vascular endothelial cells but not for vascular smooth muscle cells, which is opposite to the mitogenic activity of naturally occurring PDGF which is mitogenic for vascular smooth muscle cells but not for vascular endothelial cells, though the two are closely related. The fact that "all potential HTMPN proteins related to SEQ ID NO: 22 and polynucleotides related to SEQ ID NO: 101" as defined in the claims have a scope less than the threshold for evolutionary relatedness set forth by Brenner et al. is not relevant. What *is* relevant is that the specification as originally filed does not define a common structure or function that defines the genus claimed, and the written description is not commensurate in scope to all possible naturally occurring sequences at least 90% identical to such, which would be expected to encompass evolutionarily related, but structurally and functionally distinct, genes and proteins. It is again noted that the term "HTMPN" is defined at page 23 of the specification as being an acronym for "human transmembrane proteins." Thus, the members of the 'class' of genes or proteins denoted as "HTMPN" are defined solely by the property of being expressed in human tissue, and there is no presumption of any shared structure, function or any other physical or functional property.

C. The state of the art at the time of the present invention is further advanced than at the time of the *Lilly* and *Fiers* applications:

Appellants at p.55 of the Brief, argue that the art has matured considerably since the *Lilly* and *Fiers* cases. While this is true, it is not of consequence as regards this rejection for lack of adequate written description of the claimed genus. The key issue here is that Appellants have disclosed a single nucleic acid sequence, which is

expected to encode a single protein. No function has been attributed to either. The claims encompass all naturally occurring nucleic acid sequences that are at least 90% identical to SEQ ID NO: 101, or all nucleic acid sequences that encode proteins 90% identical to SEQ ID NO: 22. No defining characteristics have been disclosed to identify the critical features of the genus, and no species homologues or allelic variants have been described or disclosed. Further, Appellants' own arguments of evolutionary relatedness would suggest that Appellants would argue that the disclosure of a single naturally occurring sequence is sufficient written description to entitle appellant to claim the breadth of yet-undiscovered evolutionarily related but structurally and functionally distinct nucleic acids.

D. Summary:

Appellants argue that the Office has failed to base the written description inquiry "on whatever is now claimed." It is also asserted that the Office did not provide an appropriate analysis of the present claims and how they differ from those found not to satisfy the written description requirement in cases such as *Lilly* and *Fiers*. This argument is not persuasive because as indicated above (ISSUE THREE sections A and C). The claims in both those cases were limited to the naturally occurring sequences encoding particular proteins, which proteins are well known by their functions. In this case however, Appellants claim requires no such conserved function. Given that, to take the claim from *Fiers* cited by Appellants, the person of ordinary skill in the art would immediately recognize that any and all species within the metes and bounds of "A DNA which consists essentially of a DNA which codes for a human fibroblast interferon-beta

polypeptide" would encode proteins with *greater* than the 90% identity claimed by Appellants; the person of ordinary skill in the art would not expect to find that great amount of variation within a single species, while still meeting the functional limitation of being a human fibroblast interferon-beta polypeptide. Thus, the claims in both *Lilly* and *Fiers* were of *narrower* scope than the claims in question here. The key issue here is that Appellants have disclosed a single nucleic acid sequence, which is expected to encode a single protein. No function has been attributed to either. The claims encompass all naturally occurring nucleic acid sequences that are at least 90% identical to SEQ ID NO: 101, or all nucleic acid sequences that encode proteins 90% identical to SEQ ID NO: 22. No defining characteristics have been disclosed to identify the critical features of the genus, and no species homologues or allelic variants have been described or disclosed. Therefore, the claims of the instant invention are found not to satisfy the written description requirement.

Conclusion

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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